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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/523,617	01/06/2006	Jillian Cornish	11752-010US1	1861

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EXAMINER	
BRADLEY, CHRISTINA	
ART UNIT	PAPER NUMBER
1654	
MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/523,617	CORNISH ET AL.	
	Examiner	Art Unit	
	Christina Marchetti Bradley	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 December 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,11-13,23-25,35,36 and 53-61* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,11-13,23-25,35 and 36* is/are rejected.

7)☒ Claim(s) *53-61* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Notice to Comply*.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/20/2007 has been entered. Claims 1, 11-13, 23-25, 35, 36 and 53-61 are pending. Claims 4, 6-10, 14, 16, 18-22, 26, 28, and 30-34 were cancelled, and claims 53-61 were added in the amendment filed 12/20/2007.

Sequence Compliance

2. This application is objected to because the amino acid sequence of formula (I) is not associated with a sequence identifier (a SEQ ID NO) and is not included in the Sequence Listing. All sequences longer than ten nucleotides or four amino acids referenced in the specification must include a SEQ ID NO and must be included in the Sequence Listing. See MPEP § 2421-2422 and Notice to Comply.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1, 11-13, 23-25, 35 and 36 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled

in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

5. The claims were previously rejected based on the conclusion that given the breadth and composition of the genus of claimed preptin peptides, the extent to which distinguishing characteristics of the genus are disclosed, and the predictability associated with the art, the evidence indicates that ordinary artisans could not predict operability in the invention of any species other than peptides with at least 95% identical to SEQ ID NOs: 1, 2 or 3. Applicant's arguments filed 12/20/2007 have been fully considered but they are not persuasive. Only methods of administering peptides that are at least 95% identical to SEQ ID NOs: 1, 2, or 3, but not the full breadth of the claims, meet the written description provision of 35 U.S.C. §112, first paragraph.

6. On page 6 of the response filed 12/20/2007, Applicant argues that 90% identity to a 34 amino acid peptide requires identity to at least 30 of the amino acids in the sequence, and that 95% identity to a 34 amino acid peptide requires identity to at least 32 of the amino acids in the sequence. This is incorrect. Ninety percent of 34 is 30.6 and 95% of 34 is 32.3. A sequence includes an integer number of amino acids. Therefore, 31 amino acids must be identical for the peptide to be at least 90% identical to SEQ ID NOs: 1, 2, or 3, and 33 amino acids must be identical for the peptide to be at least 95% identical to SEQ ID NOs: 1, 2, or 3. Identity at 30 and 32 positions is 88.2 and 94.1% identity, respectively, which is less than 90 and 95% identity, respectively. Therefore, peptides of the genus "at least 90% identical to SEQ ID NOs: 1, 2 or 3" include peptides that differ from SEQ ID NOs: 1, 2 or 3 at one, two or three positions, and

peptides of the genus "at least 95% identical to SEQ ID NOs: 1, 2 or 3" include peptides that differ from SEQ ID NOs: 1, 2 or 3 at only one position.

7. Applicant argues on page 6 and throughout the response filed 12/20/2007, that the difference between 90 and 95% identity is only two additional variable positions and that therefore the genus of peptides requiring 90% identity is not excessively broader than the genus requiring 95% identity. This argument is unpersuasive. For the genus "at least 90% identical to SEQ ID NOs: 1, 2 or 3", up to three positions may be substituted. There are 34 options for the first substituted position, 33 options for the second and 32 for the third yielding 34x33x32 or 35,904 different combinations of substituted positions. Any of the 19 other amino acids may be substituted for the original amino acid yielding 19^3 possibilities for each of the 35,904 different combinations for a total of 35,904 x 19^3 or $2.46x10^8$ species in the genus. In contrast, for the genus "at least 95% identical to SEQ ID NOs: 1, 2 or 3", only one position may be substituted. There are 34 options for the substituted position yielding 34 different substituted positions. Any of the 19 other amino acids may be substituted for the original amino acid yielding 19 possibilities for each of the 34 different positions for a total of 34x19 or 646 species in the genus. Thus, the genus "at least 90% identical to SEQ ID NOs: 1, 2 or 3" includes six orders of magnitude more species than the genus "at least 95% identical to SEQ ID NOs: 1, 2 or 3".

8. On page 7 of the response filed 12/20/2007, Applicant argues that the specification discloses distinct preptin peptides and the areas of variability between these peptides. They argue that Applicant has disclosed three different peptides and has provided an alignment of their sequences to show conserved regions. Applicant argues that "given this information, one skilled in the art could easily obtain any species and assay its function using the *in vitro* assay described

in the specification. Furthermore, one of skill in the art would reasonably understand that this *in vitro* test could be performed, for example, in a 96-well plate, thus allowing multiple assays to be easily performed simultaneously." This argument is persuasive for the genus "at least 95% identical to SEQ ID NOs: 1, 2 or 3" but not for the genus "at least 90% identical to SEQ ID NOs: 1, 2 or 3".

9. Paragraphs 0007-0020 of the specification define preptin as an isolated peptide of 34 amino acids in length and the following formula I

DVST**123**VLPD**4**FPRYPVGKFF**56**DTW**7**QS**89**RL

wherein 1 is S or P; 2 is Q or P; 3 is A or T; 4 is D or N; 5 is Q or K; 6 is Y or F; 7 is R or K; 8 is A or T; and 9 is G or Q. SEQ ID NOs: 1, 2 and 3 correspond to the following sequences of formula I respectively:

DVST**SQA**VLPD**D**FPRYPVGKFF**QY**DTW**R**QS**AG**RL

DVST**SQA**VLPD**D**FPRYPVGKFF**KF**DTW**R**QS**AG**RL

DVST**PPT**VLPD**N**FPRYPVGKFF**QY**DTW**K**QS**TQ**RL

10. The peptides of formula I comprise 25 conserved amino acids and nine variable positions. Each variable position may be one of two amino acids. The peptides of the claimed invention are not limited to preptin peptides according to the definition in paragraph 0007. However, the guidance provided in the specification would lead the skilled artisan to select peptides that fall within the formula I genus. Given the constraint of this definition, the genus "at least 90% identical to SEQ ID NOs: 1, 2 or 3" includes 9x8x7 or 504 different combinations of substituted positions. The alternative of the two amino acids recited in formula I may be substituted for the original amino acid yielding a total of 504 species in the genus. In contrast, the genus "at least

95% identical to SEQ ID NOs: 1, 2 or 3 includes 9 different substituted peptides and a total of 9 species. Therefore, even with the constraints of the definition of formula I, the genus "at least 90% identical to SEQ ID NOs: 1, 2 or 3" includes significantly more species than the genus "at least 95% identical to SEQ ID NOs: 1, 2 or 3".

11. Contrary to Applicant's arguments, paragraphs 0007-0020 are insufficient to establish a structure-function correlation between the peptides and the claimed activity. Only a limited subset of the genus "at least 90% identical to SEQ ID NOs: 1, 2 or 3" is represented by SEQ ID NOs: 1, 2 and 3. For the variable positions 123, 8 combinations exist but only 2 (SQA and PPT) are represented by SEQ ID NOs: 1, 2 and 3. For position 4, both options are represented by SEQ ID NOs: 1, 2 and 3. For the sequence 56, 4 combinations exists but only 2 (QY and KF) are represented by SEQ ID NOs: 1, 2 and 3. For position 7, both options are represented by SEQ ID NOs: 1, 2 and 3. For the sequence 89, 4 combinations exists but only 2 (AG and TQ) are represented by SEQ ID NOs: 1, 2 and 3. SEQ ID NOs: 1, 2 and 3 are active but it is not clear from the sequence alignment which of the nine variable positions are most responsible and critical for function.

12. Applicant's statement on pages 7 and 8 that rejections regarding analogs, fragments and 60% identity is moot in light of the amendments to the claims is acknowledged and persuasive. Applicant's arguments regarding the genus of bone conditions presented on page 8 is also persuasive.

13. Claims 1, 11-13, 23-25, 35 and 36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of administering peptides that are at

least 95% identical to SEQ ID NOs: 1, 2, or 3, does not reasonably provide enablement for methods of administering peptides that are less than 95% identical to SEQ ID NOs: 1, 2 or 3. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Applicant's arguments with respect to each of the Wands factors filed 12/20/2007 have been fully considered but they are not persuasive.

The Nature of the Invention

14. The invention is drawn to methods for treating a bone condition associated with breakdown of bone tissue or bone loss, methods for increasing or maintaining bone density and methods for stimulating osteoblast growth or inhibiting osteoblast apoptosis, comprising administering peptides that are at least 90% identical to SEQ ID NOs: 1, 2, or 3.

The State of the Prior Art and its Predictability or Unpredictability

15. The rejection with respect to the state of the prior art and its unpredictability was made in the grounds that 1) there is significant unpredictability associated with peptide design and peptide structure/function relationships, and 2) the previously claimed genus of bone conditions includes conditions such as Paget's Disease which is characterized by excessive bone growth.

16. Applicant's statement on page 9 that the rejection with respect to Paget's disease is moot in view of the amendment to the claims is acknowledged and persuasive. The claims are now limited to conditions associated with the breakdown of bone tissue or bone loss whereas Paget's disease is associated with overactive bone growth that results in structurally abnormal and weaker bones.

17. Applicant's statement on page 10 with respect to the function of preptin and its therapeutic value for the treatment of a bone condition associated with a breakdown of bone issue or bone loss is acknowledged and persuasive.

18. Applicant has not addressed the general level of unpredictability in the peptide design art. A response to Applicant's arguments pertaining to preptin is presented below.

The breadth of the claims

19. The rejection with respect to breadth of the claims was made on the grounds that the claimed genus of peptides was exceptionally broad. Applicant's statement on page 10 that this reasoning is now moot in light of the amendment is not persuasive.

20. Applicant argues on page 6 and throughout the response filed 12/20/2007, that the difference between 90 and 95% identity is only two positions and that therefore the genus of peptides requiring 90% identity is not excessively broader than the genus requiring 95% identity. This argument is unpersuasive. For the genus "at least 90% identical to SEQ ID NOs: 1, 2 or 3", up to three positions may be substituted. There are 34 options for the first substituted position, 33 options for the second and 32 for the third yielding 34x33x32 or 35,904 different combinations of substituted positions. Any of the 19 other amino acids may be substituted for the original amino acid yielding 19^3 possibilities for each of the 35,904 different combinations for a total of 35,904 x 19^3 or $2.46x10^8$ species in the genus. In contrast, for the genus "at least 95% identical to SEQ ID NOs: 1, 2 or 3", only one position may be substituted. There are 34 options for the substituted position yielding 34 different substituted positions. Any of the 19 other amino acids may be substituted for the original amino acid yielding 19 possibilities for each of the 34 different positions for a total of 34x19 or 646 species in the genus. Thus, the

genus "at least 90% identical to SEQ ID NOs: 1, 2 or 3" includes six orders of magnitude more species than the genus "at least 95% identical to SEQ ID NOs: 1, 2 or 3".

The Amount of Direction or Guidance Presented and the Presence of Working Examples

21. The rejection with respect to the amount of guidance presented and the presence of working examples was made in the grounds that 1) the specification fails to provide a structure/function relationship that could enable the skilled artisan to select active preptin peptides, and 2) the specification fails to provide guidance that could enable the skilled artisan to determine which bone conditions could be treated by the preptin peptides.

22. Applicant's arguments on page 11 that the rejection with respect to insufficient guidance on how to select for active peptides is moot in light of the amendments has been considered but is not persuasive. On page 7 of the response filed 12/20/2007, Applicant argues that the specification discloses distinct preptin peptides and the areas of variability between these peptides. They argue that Applicants have disclosed three different peptides and have provided an alignment of their sequences to show conserved regions. Applicant argues that "given this information, one skilled in the art could easily obtain any species and assay its function using the *in vitro* assay described in the specification. Furthermore, one of skill in the art would reasonably understand that this *in vitro* test could be performed, for example, in a 96-well plate, thus allowing multiple assays to be easily performed simultaneously." This argument is persuasive for the genus "at least 95% identical to SEQ ID NOs: 1, 2 or 3" but not for the genus "at least 90% identical to SEQ ID NOs: 1, 2 or 3".

23. Paragraphs 0007-0020 of the specification define preptin as an isolated peptide of 34 amino acids in length and the following formula I

DVST**123**VLPD**4**FPRYPVGKFF**56**DTW**7**QS**89**RL

wherein 1 is S or P; 2 is Q or P; 3 is A or T; 4 is D or N; 5 is Q or K; 6 is Y or F; 7 is R or K; 8 is A or T; and 9 is G or Q. SEQ ID NOs: 1, 2 and 3 correspond to the following sequences of formula I respectively:

DVST**SQA**VLPD**D**FPRYPVGKFF**QY**DTW**R**QS**AG**RL

DVST**SQA**VLPD**D**FPRYPVGKFF**KF**DTW**R**QS**AG**RL

DVST**PPT**VLPD**N**FPRYPVGKFF**QY**DTW**K**QS**TQ**RL

24. The peptides of formula I comprise 25 conserved amino acids and nine variable positions. Each variable position may be one of two amino acids. The peptides of the claimed invention are not limited to preptin peptides according to the definition in paragraph 0007. However, the guidance provided in the specification would lead the skilled artisan to select peptides that fall within the formula I genus. Given the constraint of this definition, the genus "at least 90% identical to SEQ ID NOs: 1, 2 or 3" includes 9x8x7 or 504 different combinations of substituted positions. The alternative of the two amino acids recited in formula I may be substituted for the original amino acid yielding a total of 504 species in the genus. In contrast, the genus "at least 95% identical to SEQ ID NOs: 1, 2 or 3 includes 9 different substituted peptides and a total of 9 species. Therefore, even with the constraints of the definition of formula I, the genus "at least 90% identical to SEQ ID NOs: 1, 2 or 3" includes significantly more species than the genus "at least 95% identical to SEQ ID NOs: 1, 2 or 3".

25. Contrary to Applicant's arguments, paragraphs 0007-0020 are insufficient to establish a structure-function correlation between the peptides and the claimed activity. Only a limited subset of the genus "at least 90% identical to SEQ ID NOs: 1, 2 or 3" is represented by SEQ ID

NOs: 1, 2 and 3. For the variable positions 123, 8 combinations exist but only 2 (SQA and PPT) are represented by SEQ ID NOs: 1, 2 and 3. For position 4, both options are represented by SEQ ID NOs: 1, 2 and 3. For the sequence 56, 4 combinations exists but only 2 (QY and KF) are represented by SEQ ID NOs: 1, 2 and 3. For position 7, both options are represented by SEQ ID NOs: 1, 2 and 3. For the sequence 89, 4 combinations exists but only 2 (AG and TQ) are represented by SEQ ID NOs: 1, 2 and 3. SEQ ID NOs: 1, 2 and 3 are active but it is not clear from the sequence alignment which of the nine variable positions are most responsible and critical for function.

26. Applicant's statement on page 10 that one of skill in the art would clearly recognize that patients suffering from a breakdown of bone issue or bone loss could benefit from treatment with an agent that increases osteoblast activity is acknowledged and persuasive.

27. Applicant's statement on page 11 increases in bone area and/or mineralizing surface content correlate with increasing or maintaining bone density is acknowledged and persuasive.

28. Applicant's statement on page 11 that the amendment to claim 25 renders the rejection with respect to osteoblast apoptosis modulation moot is acknowledged and persuasive.

The Quantity of Experimentation Necessary

29. Considering the factors above, the skilled artisan would be burdened with undue experimentation in determining if one of the claimed peptide would be effective in the claimed methods. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation. The specification, while being enabling for methods of administering peptides that are at least 95% identical to SEQ ID NOs: 1, 2, or 3, does not reasonably provide enablement for methods of administering peptides

that are less than 95% identical to SEQ ID NOs: 1, 2 or 3. The rejection with respect to bone conditions being treated is dropped.

Allowable Subject Matter

30. Claims 53-61 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

31. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christina Marchetti Bradley whose telephone number is (571)272-9044. The examiner can normally be reached on Monday, Tuesday and Thursday, 8 A.M. to 5:30 P.M.

32. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

33. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Cecilia Tsang/
Supervisory Patent Examiner, Art Unit 4131

/Christina Marchetti Bradley/
Examiner, Art Unit 1654